Limitations to systemic and locomotor limb muscle oxygen delivery and uptake during maximal exercise in humans

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Reductions in systemic and locomotor limb muscle blood flow and O_2 delivery limit aerobic capacity in humans. To examine whether O_2 delivery limits both aerobic power and capacity, we first measured systemic haemodynamics, O_2 transport and O_2 uptake ($\dot{V}_{O_2}$) during incremental and constant (372 ± 11 W; 85% of peak power; mean ± S.E.M.) cycling exercise to exhaustion ($n = 8$) and then measured systemic and leg haemodynamics and $\dot{V}_{O_2}$ during incremental cycling and knee-extensor exercise in male subjects ($n = 10$). During incremental cycling, cardiac output ($\dot{Q}$) and systemic O_2 delivery increased linearly to 80% of peak power ($r^2 = 0.998$, $P < 0.001$) and then plateaued in parallel to a decline in stroke volume (SV) and an increase in central venous and mean arterial pressures ($P < 0.05$). In contrast, heart rate and $\dot{V}_{O_2}$ increased linearly until exhaustion ($r^2 = 0.993$; $P < 0.001$) accompanying a rise in systemic O_2 extraction to 84 ± 2%. In the exercising legs, blood flow and O_2 delivery levelled off at 73–88% of peak power, blunting leg $\dot{V}_{O_2}$ per unit of work despite increasing O_2 extraction. When blood flow increased linearly during one-legged knee-extensor exercise, $\dot{V}_{O_2}$ per unit of work was unaltered on fatigue. During constant cycling, $\dot{Q}$, SV, systemic O_2 delivery and $\dot{V}_{O_2}$ reached maximal values within ∼5 min, but dropped before exhaustion ($P < 0.05$) despite increasing or stable central venous and mean arterial pressures. In both types of maximal cycling, the impaired systemic O_2 delivery was due to the decline or plateau in $\dot{Q}$ because arterial O_2 content continued to increase. These results indicate that an inability of the circulatory system to sustain a linear increase in O_2 delivery to the locomotor muscles restrains aerobic power. The similar impairment in SV and O_2 delivery during incremental and constant load cycling provides evidence for a central limitation to aerobic power and capacity in humans.

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From rest to maximal exercise, the cardiovascular system must adjust to the increasing metabolic demand by ensuring the delivery of O_2 and substrates to all body cells, in particular to the myocytes, without compromising arterial pressure. The prevailing theory is that the cardiovascular system responds to exercise of increasing intensity up to aerobic power (maximal oxygen uptake ($\dot{V}_{O_2max}$)) by increasing systemic and contracting skeletal muscle O_2 delivery in proportion to the rise in O_2 demand, while increasing the perfusion pressure (Holmgren, 1956; Åstrand *et al.* 1964; Ekelund & Holmgren, 1967; Higginbotham *et al.* 1986; Reeves *et al.* 1990; Pawelczyk *et al.* 1992; Rowell, 1993; Rowell *et al.* 1996). However, recent findings during constant load maximal cycling exercise indicate that, following early adjustments that allow $\dot{V}_{O_2max}$ to be reached and maintained for 1–2 min, cardiac output ($\dot{Q}$), leg blood flow (LBF), perfusion pressure and O_2 delivery decline leading to reductions in $\dot{V}_{O_2max}$ and leg $\dot{V}_{O_2}$ despite increases in O_2 extraction (González-Alonso & Calbet, 2003; González-Alonso *et al.* 2004). These findings suggest that a reduction in systemic and locomotive skeletal muscle O_2 delivery limits aerobic and maximal endurance capacity in trained individuals. The question then arises whether systemic and locomotor limb muscle O_2 delivery is also impaired during incremental exercise and whether this could explain the plateau or decline in $\dot{V}_{O_2}$ observed sometimes before exhaustion (Åstrand, 1952; Taylor *et al.*

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1955; Mitchell *et al.* 1958; Froelicher *et al.* 1972; Pollock *et al.* 1976; Meyers *et al.* 1990; Knight *et al.* 1992; Day *et al.* 2003).

Indirect evidence indicates that O_2 delivery might impose a limitation to $\dot{V}_{O_2}$ at intensities close to $\dot{V}_{O_2max}$. Firstly, in humans the increase in $\dot{V}_{O_2}$ per unit of work is attenuated at high compared to low exercise intensities (Hill & Lupton, 1923; Åstrand & Saltin, 1961; Whipp & Wasserman, 1972). Secondly, the increase in $\dot{Q}$ per litre increase in $\dot{V}_{O_2}$ is attenuated at intensities above 40–70% of $\dot{V}_{O_2max}$ in humans, as in miniature swine (Saltin, 1964; Åstrand *et al.* 1964; Armstrong *et al.* 1987). These early observations lack conclusive support and are therefore not widely accepted. The general belief is that $\dot{Q}$ and O_2 delivery increase linearly from rest to $\dot{V}_{O_2max}$, implying that O_2 delivery to locomotor limb muscle does not limit $\dot{V}_{O_2}$ (Asmussen & Nielsen, 1952; Chapman *et al.* 1960; Bevegård *et al.* 1963; Rowell *et al.* 1964; Grimsby *et al.* 1966; Poliner *et al.* 1980; Higginbotham *et al.* 1986). This theory, however, is based on linear regression analysis of $\dot{Q}$ data that have not been normalized and on the assumption that systemic haemodynamics closely reflect skeletal muscle haemodynamics. At the skeletal muscle level, not only restrictions in the systemic supply of O_2, but also limitations in diffusive O_2 transport from the muscle capillary to the mitochondrial cytochrome and oxidative capacity of mitochondria could restrict $\dot{V}_{O_2max}$ (Roca *et al.* 1989). In favour of a dominant O_2 supply limitation, quadriceps muscle blood flow and $\dot{V}_{O_2}$ might reach ~2.3 and ~0.35 l kg^{-1} min^{-1} during maximal knee-extensor exercise, suggesting that only 10–15 kg of muscle needs to be recruited during whole body exercise to surpass the capacity of the human circulation to deliver O_2 (Andersen & Saltin, 1985). Whether the O_2 delivery to muscles and uptake of the quadriceps femoris are restricted during whole body compared to knee-extensor exercise remains unknown.

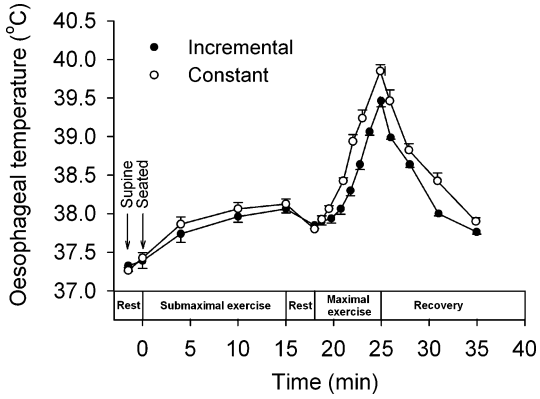

Figure 1. Core temperature during the constant and incremental protocols
Oesophageal temperature at rest, during submaximal and maximal exercise, and during 10 min of recovery, in incremental (●) and constant (○) exercise protocols. Data are means ± S.E.M. for 8 subjects.

To investigate the contribution of the O_2 transport system to $\dot{V}_{O_2max}$, we determined: (1) whether systemic O_2 delivery imposes a limitation to aerobic power and capacity, (2) whether locomotor limb blood flow and O_2 delivery are impaired during incremental exercise to exhaustion to the extent that they compromise limb $\dot{V}_{O_2}$, and (3) whether quadriceps muscle blood flow and $\dot{V}_{O_2}$ are lower during maximal exercise with a large compared to a small muscle mass. To accomplish these aims, we first measured systemic haemodynamics, O_2 transport and $\dot{V}_{O_2}$ during incremental and constant cycling exercise to exhaustion in trained male subjects and then measured systemic and exercising leg haemodynamics, O_2 transport and $\dot{V}_{O_2}$ during incremental cycle and knee-extensor exercise to exhaustion in another group of active male subjects. We hypothesized that restrictions in O_2 supply to locomotor limb muscles imposes a limitation to aerobic power and capacity in humans.

Methods

Eighteen endurance-trained or recreationally active male subjects participated in two studies. They had a mean (± S.D.) age of 27 ± 3 years, body weight of 81.3 ± 9.6 kg, height of 185 ± 9 cm, maximal heart rate (HR) of 192 ± 7 beats min^{-1} and $\dot{V}_{O_2max}$ of 4.80 ± 0.46 l min^{-1}. The subjects were informed of any risks and discomforts associated with the experiments before giving written consent to participate. The study was approved by the Ethics Committee of Copenhagen (KF 01-230/00) and conducted in accordance with the guidelines of the *Declaration of Helsinki*.

In the first study and on the first visit to the laboratory, eight endurance-trained subjects performed incremental exercise on a cycle ergometer (Excalibur, Lode, The Netherlands) to determine $\dot{V}_{O_2max}$, maximal HR and peak power. Thereafter, they completed four high-intensity training sessions on the cycle ergometer. During the last session, they carried out the same protocol as during the main experiment involving incremental (INC) and constant (CON) maximal exercise separated by one hour of recovery, while continuous measures of $\dot{V}_{O_2}$, HR and oesophageal temperature were obtained. For the invasive experiment, the subjects arrived at the laboratory one hour prior to the experiment after a light breakfast. Catheters were placed into the brachial artery and an antecubital vein, with the latter catheter being advanced to the right atrium. Following 30 min of supine rest, the subjects completed INC and CON on the cycle ergometer preceded by a 15 min warm-up period (146 ± 6 W; <50% $\dot{V}_{O_2max}$) and 3 min of rest, followed by 10 min of recovery. Throughout the protocol, the arms rested on aerobars simulating the position that cyclists adopt during a time-trial. During the resting and recovery periods, the subjects were allowed to move their legs (0 W). During INC, the workload was

increased every minute using a computerized system to elicit 20, 40, 60, 80, 90, 95 and 100% of peak power. During CON, the intensity resulted in exhaustion within 5–7 min and $\dot{V}_{O_2max}$ within 4–5 min (i.e. at 372 ± 11 W or at 85% of the 438 ± 13 W peak power of the initial incremental test). The order of the two trials was randomly assigned and counterbalanced across the subjects. Exercise was performed under thermoneutral conditions (∼20°C)

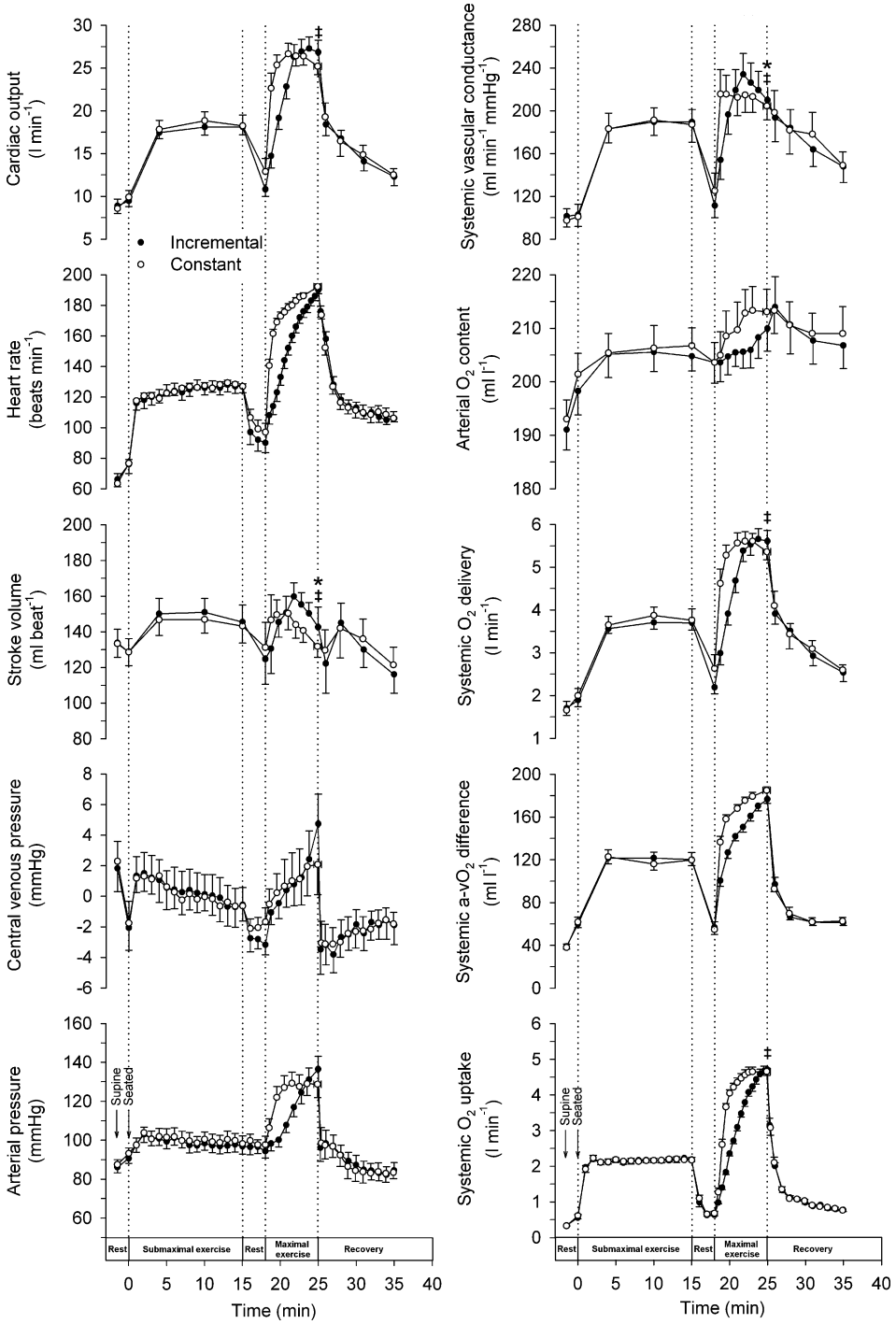

Figure 2. Central haemodynamics during the constant and incremental protocols
Cardiac output, heart rate, stroke volume, central venous and arterial pressure, systemic vascular conductance, arterial O_2 content, systemic O_2 delivery, a–v O_2 difference and $\dot{V}_{O_2}$ at rest, during submaximal and maximal exercise, and during 10 min of recovery, in incremental (●) and constant load (○) exercise. Data are means ± S.E.M. for 8 subjects, except arterial and central venous pressures and systemic vascular conductance for which data represent 7 subjects. * Lower than the value after 22 min when cycling at 80% of peak power, $P < 0.05$. ‡ Lower than the peak values observed after 20–24 min of constant load maximal cycling, $P < 0.05$.

with fans directed against the back and the side of the subjects.

Ten subjects participated in the second investigation which was aimed at determining whether convective O_2 transport and limb muscle $\dot{V}_{O_2}$ are compromised during incremental cycle exercise to exhaustion and whether quadriceps muscle blood flow and $\dot{V}_{O_2}$ are lower during maximal cycle compared to maximal knee-extensor exercise. In these subjects, an additional catheter was inserted into the femoral vein 2 cm from the inguinal ligament to allow for blood sampling and measurements of LBF (Andersen & Saltin, 1985). During both types of incremental exercise, the workload was increased every 1.5 min to elicit 25, 50, 75, 90 and 100% of peak power.

In study 1, blood samples (1–5 ml) were drawn simultaneously from the brachial artery and the right

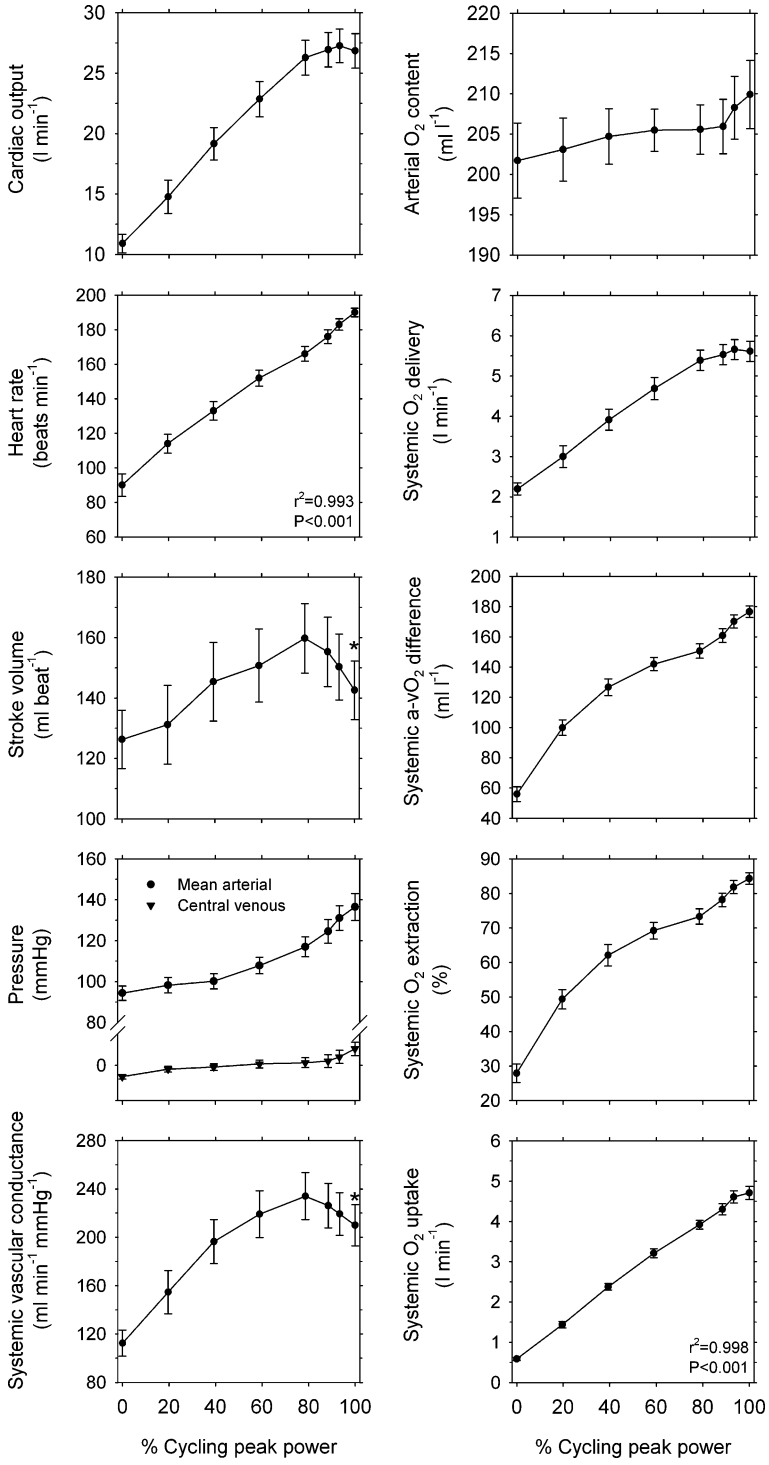

Figure 3. Central haemodynamics during incremental exercise to exhaustion
Cardiac output, heart rate, stroke volume, arterial (●) and central venous (▼) pressure, systemic vascular conductance, arterial O_2 content, systemic O_2 delivery, systemic a–v O_2 difference, systemic O_2 extraction and pulmonary $\dot{V}_{O_2}$ during incremental exercise to exhaustion plotted against the relative increase in power output. Data are means ± S.E.M. for 8 subjects. * Lower than 80% of peak power, $P < 0.05$.

atrium at rest in the supine and upright positions, during the warm-up (4, 10 and 15 min), immediately before the start of maximal exercise, during maximal exercise and during the recovery (1, 3, 6 and 10 min). In INC, blood samples were drawn after 45 s of each workload and at exhaustion. In CON, they were drawn after 0.75, 1.5, 3, 4 and 5 min and before exhaustion. In study 2, blood samples were drawn simultaneously from the brachial artery, right atrium and the femoral vein after 45 s at each workload, and LBF was measured after 1 min.

Throughout the studies, pulmonary $\dot{V}_{O_2}$ was measured online (Medgraphics CPX/D, Saint Paul, MN, USA; study 1 and Cosmed Quark b^2, Italy; study 2). During the invasive experiments, HR was obtained from an electrocardiogram while arterial and central venous pressures were monitored with transducers positioned at heart level (Pressure Monitoring Kit, Baxter). The LBF was measured by the constant-infusion thermodilution method (Andersen & Saltin, 1985; González-Alonso *et al.* 2000*b*), while $\dot{Q}$ was calculated using the Fick principle ($\dot{Q} = \dot{V}_{O_2}$/arteriovenous (a–v) O_2 difference), assuming negligible differences in blood oxygenation between the right atrium and the pulmonary artery (Barratt-Boyes & Wood, 1956). The $\dot{Q}$ data obtained in one subject using the direct Fick principle confirmed the $\dot{Q}$ results. Stroke volume (SV) was the quotient between $\dot{Q}$ and HR, and systemic and leg vascular conductance were the quotients between $\dot{Q}$ and LBF and the perfusion pressure. Perfusion pressure was the difference between mean arterial (MAP) and central venous pressures and pulse pressure was that between the systolic and diastolic blood pressure. The left ventricular contractility index dP/dt_{max} was calculated as the peak systolic value of the first derivative of the arterial pressure curve over 20 cardiac cycles. For systemic O_2 delivery, $\dot{Q}$ was multiplied by the arterial O_2 content whereas systemic O_2 extraction was the ratio between the systemic a–v O_2 difference and the arterial O_2 content. Blood gases, haemoglobin, glucose and lactate concentrations were measured using an ABL700 analyser (Radiometer, Copenhagen, Denmark). Oesophageal temperature was measured with a thermocouple (MOV-A, Ellab, Copenhagen, Denmark) inserted through the nasal passage at a distance equal to one-fourth of the subject's standing height, and HR was measured with a Polar Sports Tester (Polar Electro). In study 1, blood gas variables were corrected for the temperature measured during the non-invasive trials, whereas in study 2 the correction was made from the femoral venous blood temperature. Leg muscle mass was calculated from the whole-body dual-energy X-ray absorptiometry scanning (Prodigy, General Electrics Medical Systems, WI, USA) as lean mass of the region. Quadriceps femoris muscle mass was calculated using the antropomethic method, as described by Anderson & Saltin, 1985.

Statistical analysis

A one-way repeated measures analysis of variance (ANOVA) was performed to test significance within and between the two trials. Following a significant *F* test, pair-wise differences were identified using Tukey's honestly significant difference (HSD) *post hoc* procedure. To determine whether exhaustion during the constant maximal exercise was preceded by reductions in $\dot{Q}$, SV and O_2 delivery, final values were compared with peak values during exercise using one-way repeated measures ANOVA with Tukey's HSD *post hoc* procedure. The significance level was set at $P < 0.05$ and data are means ± S.E.M. unless indicated otherwise.

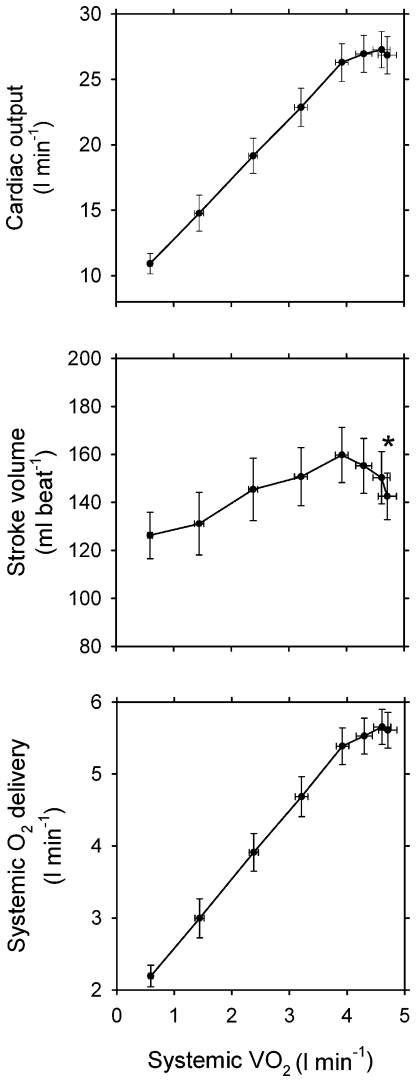

Figure 4. Relationship between cardiac output and systemic $\dot{V}_{O_2}$ during incremental exercise to exhaustion
Cardiac output, stroke volume and systemic O_2 delivery plotted against the increases in $\dot{V}_{O_2}$ during incremental exercise. The plateau in cardiac output was due to a concomitant decline in stroke volume. Data are means ± S.E.M. for 8 subjects. * Lower than the stroke volume value observed at a systematic $\dot{V}_{O_2}$ of 3.9 L min^{-1} when cycling at 80% of peak power, $P < 0.05$.

Table 1. Blood variables at rest, during incremental exercise to exhaustion, and after 10 min of recovery

		Incremental exercise (% peak power)							
	Rest	20%	40%	60%	80%	90%	95%	100%	10 min recovery
Haemoglobin (g l^{-1})									
a	150 ± 4	153 ± 3	155 ± 3	156 ± 2*	157 ± 2*	158 ± 3*	160 ± 3*	162 ± 3*	156 ± 3*
v	151 ± 4	151 ± 4	152 ± 4	153 ± 4	158 ± 3*	159 ± 3*	161 ± 4*	163 ± 4*	154 ± 3
P_{O_2} (mmHg)									
a	120 ± 4	101 ± 2*	95 ± 2*	92 ± 4*	91 ± 3*	93 ± 3*	96 ± 3*	102 ± 3*	118 ± 2
v	40 ± 2	30 ± 2*	26 ± 1*	22 ± 1*	21 ± 1*	20 ± 1*	20 ± 1*	21 ± 1*	48 ± 2*
O_2 saturation (%)									
a	98.8 ± 0.1	98.0 ± 0.1	97.5 ± 0.2*	97.1 ± 0.3*	96.6 ± 0.3*	96.2 ± 0.3*	95.4 ± 0.5*	95.0 ± 0.5*	97.3 ± 0.2*
v	71.3 ± 2.3	50.4 ± 2.7*	37.6 ± 3.0*	30.4 ± 2.1*	25.6 ± 2.1*	20.9 ± 1.8*	17.2 ± 1.7*	14.8 ± 1.5*	69.8 ± 1.2
O_2 content (ml l^{-1})									
a	202 ± 5	203 ± 4	205 ± 3	205 ± 3	206 ± 3	206 ± 3	208 ± 4	210 ± 4*	207 ± 4
v	146 ± 7	103 ± 7*	78 ± 7*	63 ± 5*	55 ± 5*	45 ± 4*	38 ± 4*	33 ± 4*	146 ± 5
P_{CO_2} (mmHg)									
a	41 ± 1	42 ± 1	42 ± 1	42 ± 0	42 ± 1	41 ± 1	39 ± 1	37 ± 1*	33 ± 1*
v	50 ± 1	53 ± 1	56 ± 1	61 ± 1*	70 ± 1*	77 ± 2*	83 ± 2*	87 ± 3*	43 ± 1*
pH									
a	7.40 ± 0.01	7.40 ± 0.00	7.39 ± 0.00	7.38 ± 0.01	7.36 ± 0.01*	7.32 ± 0.01*	7.26 ± 0.01*	7.20 ± 0.01*	7.19 ± 0.01*
v	7.35 ± 0.01	7.35 ± 0.00	7.33 ± 0.01	7.30 ± 0.01*	7.24 ± 0.01*	7.17 ± 0.01*	7.10 ± 0.01*	7.03 ± 0.01*	7.16 ± 0.01*
Lactate (mmol l^{-1})									
a	1.0 ± 0.1	1.0 ± 0.1	1.3 ± 0.1	2.0 ± 0.2	4.2 ± 0.3*	7.7 ± 0.3*	11.9 ± 0.4*	16.4 ± 0.7*	14.3 ± 0.6*
v	1.0 ± 0.1	1.0 ± 0.1	1.7 ± 0.4	2.4 ± 0.4	4.3 ± 0.3*	8.0 ± 0.4*	12.1 ± 0.5*	16.8 ± 0.8*	13.7 ± 0.8*
Glucose (mmol l^{-1})									
a	5.3 ± 0.3	5.3 ± 0.3	5.3 ± 0.3	5.4 ± 0.3	5.3 ± 0.3	5.2 ± 0.3	5.2 ± 0.3	5.0 ± 0.3	6.2 ± 0.2*
v	5.2 ± 0.3	5.2 ± 0.3	5.2 ± 0.3	5.2 ± 0.3	5.3 ± 0.3	5.2 ± 0.3	5.1 ± 0.3	4.9 ± 0.3	6.1 ± 0.2*

Values are means ± S.E.M. for 8 subjects. a, arterial. v, right atrium. * Different from rest, $P < 0.05$. P_{O_2}, P_{CO_2} and pH values were corrected for changes in blood temperature.

Results

Performance and maximal O_2 uptake

No significant differences in endurance, $\dot{V}_{O_2max}$ or peak power were observed between the non-invasive and the invasive experiments. In INC, time to fatigue was 6.45 ± 0.2 and 6.96 ± 0.1 min during the non-invasive and invasive experiments, respectively, accompanied by a similar $\dot{V}_{O_2max}$ (4.81 ± 0.12 and 4.75 ± 0.15 l min^{-1}, respectively) and peak power (440 ± 16 and 446 ± 13 W, respectively). Similarly, in CON, time to fatigue was 7.01 ± 0.23 and 6.87 ± 0.50 min during the non-invasive and invasive experiments, respectively, and $\dot{V}_{O_2max}$ was 4.82 ± 0.12 *versus* 4.75 ± 0.13 l min^{-1}. In INC the workload elicited 20 ± 0, 39 ± 0, 59 ± 1, 79 ± 1, 88 ± 15, 93 ± 1 and 100 ± 0% of peak power during the invasive experiment. Oesophageal temperature increased from ∼37.8°C at the onset of exercise to 39.5 ± 0.1 and 39.9 ± 0.1°C in INC and CON, respectively (Fig. 1).

Systemic haemodynamics, O_2 transport and O_2 uptake

No differences in systemic haemodynamics, O_2 transport or $\dot{V}_{O_2}$ were observed at rest or during the 15 min of submaximal exercise (Fig. 2). In INC, $\dot{Q}$ increased linearly to 80% of peak power ($r^2 = 0.998$; $P < 0.001$) and then plateaued (Figs 2–4). In CON, $\dot{Q}$ increased during the first 1.5 min, reached a peak value of 27.1 ± 1.1 l min^{-1} after 4.6 ± 0.6 min (range 3–6 min) and then declined 1.9 ± 0.5 l min^{-1} before exhaustion ($P < 0.05$). The observed plateau in $\dot{Q}$ above 80% of peak power in INC and the drop during CON were due to a fall in SV (20 ± 3 and 27 ± 6 ml $beat^{-1}$ in INC and CON, respectively), because HR continued to increase to exhaustion (190 ± 2 and 192 ± 2 beats min^{-1}, respectively). In both INC and CON, central venous pressure increased from −3 mmHg at rest to 2–5 mmHg at exhaustion. In INC, MAP increased from 94 ± 4 mmHg at the start of exercise to 136 ± 7 mmHg at exhaustion. In contrast, in CON, MAP stabilized at ∼128 mmHg after 1.5 min. In INC, perfusion pressure increased from 98 ± 3 to 131 ± 6 mmHg at exhaustion accompanying an increase in pulse pressure from 59 ± 4 to 144 ± 4 mmHg. In contrast, perfusion pressure in CON increased from 100 ± 4 to 127 ± 6 mmHg after 3 min and remained stable thereafter. Similarly, pulse pressure increased from 60 ± 3 to 137 ± 4 mmHg after 3 min. In INC, systemic vascular conductance increased to ∼80% of peak power (range 60–90%) and then declined ($P < 0.05$). In CON, vascular conductance

Table 2. Blood variables at rest, during constant load maximal exercise, and after 10 min of recovery

		Constant load exercise (min)						
	Rest	0.8	1.5	3	4	5	6.9 ± 0.5	10 min recovery
Haemoglobin (g l^{-1})								
a	151 ± 3	155 ± 3	159 ± 3*	160 ± 4*	165 ± 3*	166 ± 3*	169 ± 3*	158 ± 4*
v	155 ± 3	158 ± 3	161 ± 4	163 ± 3	165 ± 3*	166 ± 3*	165 ± 3*	157 ± 5
P_{O_2} (mmHg)								
a	118 ± 4	91 ± 4*	91 ± 3*	92 ± 4*	94 ± 4*	96 ± 4*	101 ± 4*	117 ± 3
v	40 ± 1	22 ± 1*	20 ± 1*	20 ± 1*	20 ± 1*	20 ± 1*	20 ± 1*	49 ± 2*
O_2 saturation (%)								
a	98.8 ± 0.2	97.1 ± 0.5	96.6 ± 0.3*	96.1 ± 0.6*	94.7 ± 0.6*	94.3 ± 0.9*	93.0 ± 1.0*	96.9 ± 0.4*
v	70.8 ± 2.4	31.7 ± 2.8*	22.9 ± 2.3*	18.7 ± 1.7*	16.6 ± 1.6*	15.1 ± 1.8*	12.5 ± 1.2*	68.8 ± 1.3
O_2 content (ml l^{-1})								
a	204 ± 4	205 ± 4	209 ± 5	209 ± 6	213 ± 4*	213 ± 4*	213 ± 4*	209 ± 5
v	149 ± 7	68 ± 7*	50 ± 6*	42 ± 4*	37 ± 4*	34 ± 4*	29 ± 3*	146 ± 5
P_{CO_2} (mmHg)								
a	41 ± 1	41 ± 1	41 ± 1	38 ± 1	37 ± 1	36 ± 1*	34 ± 1*	33 ± 1*
v	51 ± 1	58 ± 2*	71 ± 2*	76 ± 2*	78 ± 2*	79 ± 2*	82 ± 3*	43 ± 1*
pH								
a	7.41 ± 0.01	7.39 ± 0.01	7.35 ± 0.01	7.27 ± 0.01*	7.23 ± 0.01*	7.20 ± 0.01*	7.12 ± 0.02*	7.17 ± 0.03*
v	7.35 ± 0.00	7.32 ± 0.01	7.22 ± 0.01*	7.13 ± 0.01*	7.09 ± 0.01*	7.06 ± 0.01*	7.00 ± 0.02*	7.14 ± 0.03*
Lactate (mmol l^{-1})								
a	1.1 ± 0.1	1.9 ± 0.2	5.3 ± 0.4*	10.8 ± 0.6*	13.7 ± 0.8*	16.0 ± 0.9*	19.0 ± 1.1*	13.8 ± 1.2*
v	1.0 ± 0.1	2.2 ± 0.2	5.4 ± 0.5*	10.8 ± 0.6*	13.4 ± 0.7*	15.6 ± 0.9*	18.6 ± 1.1*	13.6 ± 1.2*
Glucose (mmol l^{-1})								
a	5.4 ± 0.2	5.3 ± 0.2	5.4 ± 0.2	5.3 ± 0.3	5.2 ± 0.3	5.2 ± 0.3	5.3 ± 0.2	7.3 ± 0.3*
v	5.3 ± 0.2	5.3 ± 0.2	5.3 ± 0.2	5.3 ± 0.2	5.2 ± 0.3	5.2 ± 0.2	5.2 ± 0.2	7.2 ± 0.3*

Values are means ± S.E.M. for 8 subjects. a, arterial. v, right atrium. * Different from rest, $P < 0.05$. P_{O_2}, P_{CO_2} and pH values were corrected for changes in blood temperature.

reached a plateau (range 0.75–3 min) and then declined ($P < 0.05$). No difference in dP/dt_{max} was observed at peak SV and exhaustion in either INC (2287 ± 96 *versus* 2419 ± 77 mmHg s^{-1}; $P = 0.35$) or CON (2119 ± 271 *versus* 2193 ± 230 mmHg s^{-1}; $P = 0.72$).

In both INC and CON, there was an increase in haemoglobin concentration, resulting in an elevated arterial O_2 content, despite declining arterial O_2 tension and saturation (Tables 1 and 2; Fig. 2). In INC, systemic O_2 delivery increased linearly to 80% of peak power ($r^2 = 0.998$; $P < 0.001$) and then levelled off (Figs 2–4). In CON, systemic O_2 delivery increased to reach a maximal value of 5.7 ± 0.2 l min^{-1} after 4.4 ± 0.4 min (range 3–5 min) and then declined 0.35 ± 0.08 l min^{-1} before exhaustion ($P < 0.05$). During both INC and CON, systemic a–v O_2 difference and O_2 extraction increased until exhaustion. At exhaustion in INC and CON, systemic O_2 extraction was 84 ± 2% and 87 ± 1%, respectively. In INC, $\dot{V}_{O_2}$ increased linearly to exhaustion and therefore $\dot{V}_{O_2max}$ was reached during the last ~0.5 min ($r^2 = 0.998$; $P < 0.001$; Fig. 3). In CON, $\dot{V}_{O_2max}$ was reached within 4–6 min, maintained for 2.0 ± 0.3 min, but declined 0.14 ± 0.05 l min^{-1} before exhaustion ($P < 0.05$).

Leg haemodynamics, O_2 transport and O_2 uptake

The rate of increase in LBF and O_2 delivery during incremental exercise was attenuated at intensities above 50% of peak power, reaching a plateau at 73–88% (Fig. 5). The levelling off in LBF, associated with a plateau in leg vascular conductance, attenuated the increase in leg $\dot{V}_{O_2}$ (8.8 ± 0.5 *versus* 11.9 ± 0.7 ml W^{-1} min^{-1} at exhaustion compared to 50% peak power, respectively; $P = 0.003$), despite increasing O_2 extraction. At the systemic level, $\dot{Q}$ reached a plateau at ~80% peak power leading to the blunting of the rate of increase in O_2 delivery per litre of $\dot{V}_{O_2}$ (Fig. 6). In contrast to incremental cycling, LBF, O_2 delivery and leg $\dot{V}_{O_2}$ increased linearly from rest to exhaustion during one-legged knee-extensor exercise ($r^2 = 0.994$–0.999; $P < 0.0002$), thereby allowing the maintenance of constant LBF, leg O_2 delivery and leg $\dot{V}_{O_2}$ per unit of work (slopes = 75.6, 16.3 and 13.4 ml W^{-1} min^{-1}, respectively). As depicted in Fig. 7, LBF and leg $\dot{V}_{O_2}$ were higher during maximal cycling compared to knee-extensor exercise. However, leg $\dot{V}_{O_2}$ was lower during cycle compared to knee-extensor exercise when expressed per unit of work (8.8 ± 0.5 *versus* 12.2 ± 0.6 ml W^{-1} min^{-1}, respectively;

$P < 0.01$) or estimated active muscle mass (175 ± 9 *versus* 443 ± 34 ml kg^{-1} min^{-1}, respectively; $P < 0.01$) due largely to the lower blood flow.

Discussion

This study employed two-legged cycling and one-legged knee-extension as exercise models for investigating whether O_2 transport poses a limitation to aerobic power and capacity in humans. The key observations were: (1) during incremental cycling, $\dot{Q}$, LBF and O_2 delivery reached a plateau at intensities below $\dot{V}_{O_2max}$, accompanying a decline in SV and increases in central venous pressure and MAP, (2) with a blunted LBF, leg $\dot{V}_{O_2}$ per unit of work declined despite the increasing O_2 extraction, (3) when LBF increased linearly during knee-extensor exercise, $\dot{V}_{O_2}$ per unit of work was unaltered, (4) during constant load cycling, SV, $\dot{Q}$, and systemic O_2 delivery and $\dot{V}_{O_2}$ dropped before exhaustion, despite increasing or stable central venous pressure, MAP and O_2 extraction, and (5) the impaired O_2 supply during cycling was due to a fall in SV, as both the arterial O_2 content and HR continued to increase. These results indicate that an inability of the circulatory system to sustain a linear increase in O_2 delivery to the locomotor limb muscles markedly restrains aerobic power. Moreover, the impaired SV and O_2 delivery during cycling together with the higher muscle $\dot{V}_{O_2}$ with unrestricted circulation during knee-extensor exercise support a preponderant central limitation to aerobic power and capacity in humans.

During incremental cycling exercise, $\dot{Q}$ and systemic O_2 delivery increased linearly to ~80% of peak power but levelled off thereafter. Similarly, the initial linear increase in LBF and O_2 delivery was attenuated at intensities above 50% of peak power, reaching a plateau at 73–88%. The tight 1 : 1 relationship between systemic and locomotor limb O_2 delivery *versus* $\dot{V}_{O_2}$ at low and moderate exercise intensities was therefore blunted at intensities above ~80% of peak power. This novel finding refutes the theory

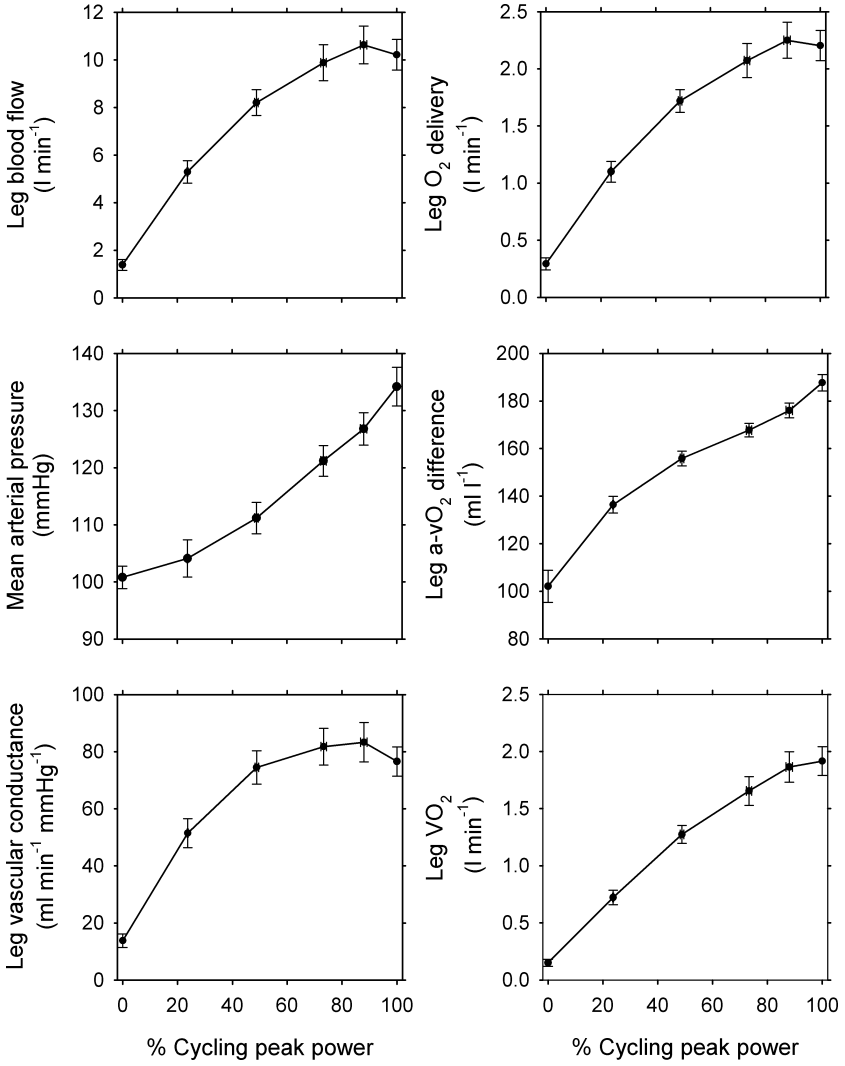

Figure 5. Leg haemodynamics during incremental exercise to exhaustion
Leg blood flow, mean arterial pressure, leg vascular conductance, leg O_2 delivery, leg a–v O_2 difference and leg $\dot{V}_{O_2}$ during incremental exercise to exhaustion plotted against the relative increase in power. Data are means ± S.E.M. for 10 subjects.

that O_2 delivery is linearly related to $\dot{V}_{O_2}$ from rest to $\dot{V}_{O_2max}$. This concept is based on linear regression analysis of: (1) $\dot{Q}$ data that were not normalized (Asmussen & Nielsen, 1952; Chapman *et al.* 1960; Bevegård *et al.* 1963; Åstrand *et al.* 1964; Saltin, 1964; Grimsby *et al.* 1966), (2) haemodynamic data from longitudinal studies on human subjects undergoing changes in physical activity levels (Saltin *et al.* 1968), (3) cross-sectional data from subjects with different training status with the focus of the analysis on whether $\dot{Q}$ could explain the differences in $\dot{V}_{O_2max}$ between well-trained and sedentary people (Ekblom & Hermansen, 1968; Ekblom, 1968), and (4) haemodynamic data in untrained humans who might have failed to attain maximal levels of exertion (Poliner *et al.* 1980; Higginbotham *et al.* 1986). Although these studies collectively documented a tight relationship between $\dot{Q}$ and $\dot{V}_{O_2}$ over a wide range of aerobic capacities, they provide neither insight into the relationship between systemic O_2 delivery and $\dot{V}_{O_2}$ close to maximal exercise, nor specific information on the contribution of locomotor limb muscle O_2 transport to $\dot{V}_{O_2max}$. The present findings in healthy trained subjects show that systemic and locomotor limb blood flow and O_2 delivery are linearly related to $\dot{V}_{O_2}$ up to 50–90% of $\dot{V}_{O_2max}$, levelling off before $\dot{V}_{O_2max}$ is reached. The critical consequence of the plateau in locomotor limb O_2 delivery is the attenuation in the rate of rise in $\dot{V}_{O_2}$ despite increasing O_2 extraction.

Restrictions in systemic and locomotor limb muscle O_2 transport pose a more important limitation to $\dot{V}_{O_2max}$ and maximal endurance capacity than suspected. In the exercising legs, $\dot{V}_{O_2}$ per unit of work declined from $11.9 \pm 0.7\,ml\,W^{-1}\,min^{-1}$ at 50% peak power to $8.8 \pm 0.5\,ml\,W^{-1}\,min^{-1}$ at exhaustion, suggesting that the concomitant exponential rise in leg lactate release accompanied a suppression in skeletal muscle aerobic ATP production. The estimate that leg O_2 delivery and $\dot{V}_{O_2}$ would have been ~52% higher (i.e. both $\sim 1\,l\,min^{-1}$) during cycling exercise if LBF increased linearly until exhaustion, illustrates the magnitude of the blunting of LBF and its effect on locomotor muscle $\dot{V}_{O_2}$. Limitations in diffusive O_2 transport from the muscle capillary to the mitochondrial cytochrome and/or oxidative capacity of mitochondria could also be restricting muscle $\dot{V}_{O_2}$ based on the observation that leg O_2 extraction is not maximal at exhaustion (Roca *et al.* 1989). Yet, an increase in leg O_2 extraction from the measured value of 87% to a hypothetical 100% would only increase leg $\dot{V}_{O_2}$ by 16% (i.e. $\sim 0.3\,l\,min^{-1}$), although this is an overestimation given that ~20% of the leg consists of non-muscle tissues with lower O_2 extraction than contracting muscle.

A critical question is whether the leg muscles can indeed increase $\dot{V}_{O_2}$ above the levels observed during maximal cycling exercise. An approach to answer this question is to determine whether quadriceps $\dot{V}_{O_2}$ is elevated when systemic O_2 transport is not limiting during maximal one-legged knee-extensor exercise (Andersen & Saltin, 1985). In contrast to cycling and in agreement with published reports (Andersen & Saltin, 1985; Richardson *et al.* 1993), leg $\dot{V}_{O_2}$ increased linearly during knee-extensor exercise to exhaustion in parallel with the rise in LBF. Leg $\dot{V}_{O_2}$ per unit of work at fatigue was therefore higher during knee-extensor than cycling exercise (Fig. 7). Moreover, assuming that the quadriceps femoris and all leg muscles are active during knee-extensor and cycling exercise, we estimated that $\dot{V}_{O_2}$ per kilogram of muscle was 3-fold higher during knee-extensor than cycling exercise (Richardson & Saltin 1998). Despite

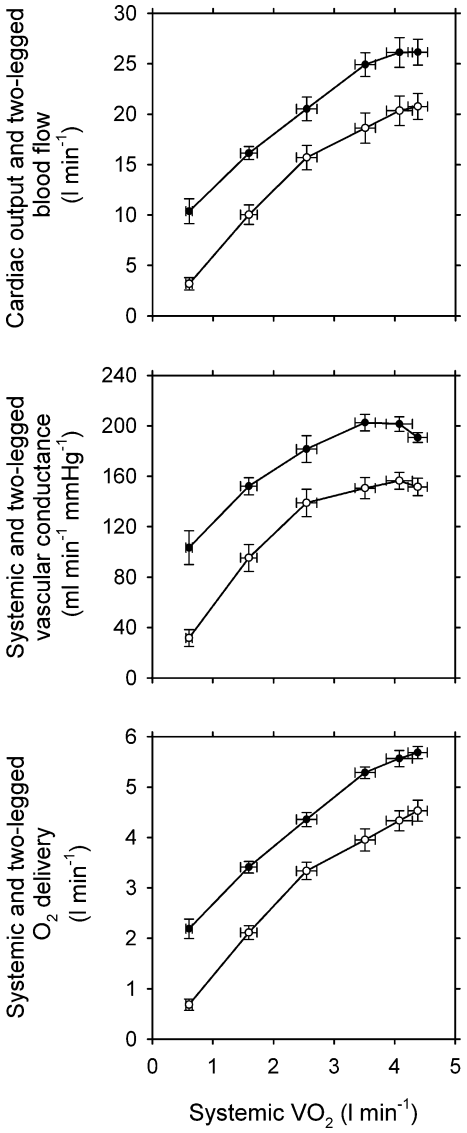

Figure 6. Relationship between blood flow, vascular conductance and O_2 delivery and $\dot{V}_{O_2}$
Cardiac output and 2-legged blood flow, systemic and 2-legged vascular conductance, and systemic and 2-legged O_2 delivery plotted against the increases in $\dot{V}_{O_2}$ during incremental exercise to exhaustion. Data are means ± S.E.M. for 6 subjects.

the uncertainty of the assumption, it is clear that the quadriceps muscles as the only muscles generating power during knee-extensor exercise, are consuming more O_2 (i.e. 1.3 l min^{-1}; 103 W; ∼2.9 kg) than they are as mere contributors to power generation during cycling (i.e. 2.0 l min^{-1}; 225 W; ∼11.4 kg). Collectively, these observations reveal that during maximal whole body exercise: (1) locomotor muscle $\dot{V}_{O_2}$ and exercise endurance could be improved if blood flow increased linearly, (2) the rates of mitochondrial oxidation and O_2 transport from capillary to mitochondrial cytochrome are not maximal, and (3) convective O_2 transport to contracting skeletal muscle fibres is severely restricted owing to the lower blood flow.

During incremental cycling, $\dot{Q}$ and LBF plateaued at ∼80% peak power in parallel to a marked blunting of systemic and leg vascular conductance, indicating an enhanced sympathetic vasoconstrictor activity. This agrees with the plateau in LBF at high cycling intensities in humans (Knight *et al.* 1992; Rosenmeier *et al.* 2004) and the plateau in $\dot{Q}$ and skeletal muscle blood flow before exhaustion in miniature swine running on a treadmill (Armstrong *et al.* 1987), but contrasts with the linear increase in LBF during one-legged knee-extensor exercise in humans when the systemic circulation is not compromised (Andersen & Saltin, 1985; Richardson *et al.* 1993). It therefore seems that during exercise with a large muscle mass, reflexes signalling the plateau in $\dot{Q}$ override the local vasodilatory stimuli responsible for the partial or full linear increase in LBF with incremental cycling and knee-extensor exercise, respectively. In support of this, a human study showed that the blunting of LBF and vascular conductance at high cycling intensities is associated with an exponential rise in circulating noradrenaline outstripping the increase of the vasodilator ATP (Rosenmeier *et al.* 2004). It is likely that the upper body limb and postural muscles as well as the heart and respiratory muscles become more active, thereby contributing to the linear increase in systemic $\dot{V}_{O_2}$ above 80% peak power. This scenario implies that the upper body muscles and organs are competing with the exercising legs for the available $\dot{Q}$ (Harms *et al.* 1997, 1998). However, the redistribution of blood flow to upper body muscles and organs ought to be small as the plateau in $\dot{Q}$ accounts for the majority of the LBF response. On the other hand, perfusion pressure did not reduce LBF as MAP increased until exhaustion. Consequently, the suppression in blood flow to the exercising legs during cycling appears to be, for the most part, the result of the blunted $\dot{Q}$ and the overriding sympathetic vasoconstrictor activity to the muscle microvasculature (Pawelczyk *et al.* 1992).

The similar maximal haemodynamic responses and blunting of O_2 transport before exhaustion during INC and CON provide further insight into the limits of cardiovascular regulation in exercising humans. Even though $\dot{V}_{O_2max}$ was maintained over a longer period during constant load cycling, both types of maximal exercise were characterized by essentially the same peak $\dot{Q}$ (27 and 28 l min^{-1} for INC and CON, respectively), HR (190 and 192 beats min^{-1}), MAP (129 and 136 mmHg), systemic O_2 delivery (5.7 and 5.8 l min^{-1}), systemic O_2 extraction (84 and 87%) and $\dot{V}_{O_2max}$ (4.8 l min^{-1}). This indicates that the limits of the cardiovascular system and a true $\dot{V}_{O_2max}$ were reached during both types of cycling. Five

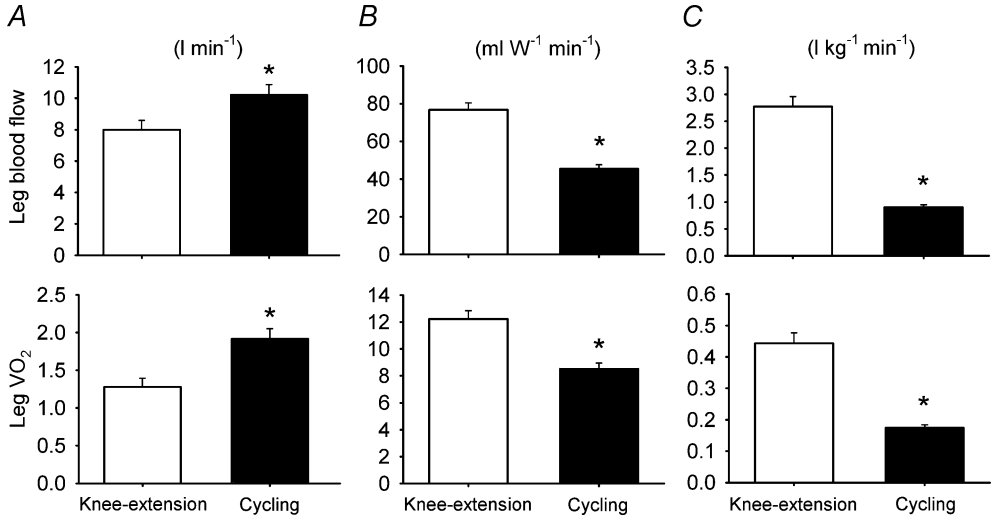

Figure 7. Quadriceps muscle perfusion and $\dot{V}_{O_2}$ during maximal knee-extensor and cycling exercise
Maximal values for leg blood flow and $\dot{V}_{O_2}$ during maximal knee-extensor and cycling exercise expressed as absolute values (*A*), in relation to peak power (*B*; 103 ± 4 and 225 ± 10 W, respectively), and in relation to the estimated active muscle mass (*C*), assuming that all quadriceps muscles (2.9 kg) and all leg muscles (11.4 kg) were recruited during maximal knee-extensor and cycling exercise, respectively. Data are means ± S.E.M. for 10 subjects. * Different from knee-extensor exercise, $P < 0.05$.

decades ago, Mitchell *et al.* (1958) provided data on the determinants of $\dot{V}_{O_2max}$. Arguing in favour of a limiting $\dot{Q}$, they found a lower $\dot{Q}$ during supramaximal compared to maximal exercise (18.2 *versus* 21.0 l min^{-1}, respectively), but $\dot{V}_{O_2max}$ was the same (2.81 *versus* 2.87 l min^{-1}; $n = 6$) because of the widening of the systemic a–v O_2 difference. Our study extends previous work by simultaneously looking at the dynamics of the central and exercising limb circulations, allowing an assessment of the contribution of the locomotor muscle to $\dot{V}_{O_2max}$. Because LBF and $\dot{V}_{O_2}$ are impaired during maximal constant load cycling (González-Alonso & Calbet, 2003), we surmise that the locomotor skeletal muscles are the main tissue accounting for the restrictions in peripheral blood flow and O_2 delivery during INC and CON.

Within the central circulation, the impaired O_2 supply was associated with a fall in SV (20–27 ml beat^{-1}), as both arterial O_2 content and HR continued to increase. This is congruent with reports during constant and incremental exercise showing a decline in SV (Keul *et al.* 1981; Higginbotham *et al.* 1986; Spina *et al.* 1992; Seals *et al.* 1994; Proctor *et al.* 1998; McCole *et al.* 1999; González-Alonso & Calbet, 2003; González-Alonso *et al.* 2004), but contrasts with the bulk of studies using incremental exercise showing either a plateau or an increase in SV with continuously increasing $\dot{Q}$ from moderate to peak exercise (Åstrand *et al.* 1964; Poliner *et al.* 1980; Rubal *et al.* 1986; Spina *et al.* 1992; Gledhill *et al.* 1994; Seals *et al.* 1994; Fleg *et al.* 1994; Proctor *et al.* 1998). Differences in exercise protocols, levels of exertion, exercise mode, sex, age and training status might account for the discrepancy in the SV responses.

The decline in SV described here could be attributed to alterations in cardiac preload, left ventricular afterload and/or left ventricular contractility (Rowell, 1974, 1993; Poliner *et al.* 1980; Higginbotham *et al.* 1986). However, a decline in preload does not seem to be a factor because in both trials central venous pressure continued to increase until exhaustion. Enhanced afterload might not be an important factor either, since SV increased early in exercise in parallel with increases in systolic blood pressure and MAP in both INC and CON and declined to a greater extent during CON when systolic blood pressure and MAP were maintained. Lastly, a depression in left ventricular contractility reducing SV is at odds with the finding that dP/dt_{max} at peak SV and at exhaustion were not different. The rate–pressure product of HR and MAP increased until exhaustion in both maximal tests, indicating that myocardial O_2 demand was rising when SV declined. In this setting, an increase in myocardial $\dot{V}_{O_2}$ can only occur by an increase in O_2 delivery provided by augmented coronary blood flow because the O_2 extraction reserve is minimal. The impaired circulation and aerobic energy turnover in skeletal muscle raises the daunting possibility that alterations in cardiac metabolism contribute to the SV decline.

Alternatively, the observation that SV declined at a HR of 170–180 beats min^{-1} during both INC and CON raises the possibility that severe tachycardia reduces SV. Studies in humans and dogs manipulating HR by pacing the heart demonstrate that severe tachycardia leads to disproportional reductions in diastolic filling time and left ventricular end-diastolic volume which compromise SV and $\dot{Q}$ (Templeton *et al.* 1972; Weisfeldt *et al.* 1978; Parke & Case, 1979; Sheriff *et al.* 1993). Consistent with the increase in core temperature to 39–40°C, human studies demonstrate that hyperthermia-induced tachycardia reduces SV during exercise (Fritzsche *et al.* 1999; González-Alonso *et al.* 1997, 1999, 2000*a*) and that blunting core hyperthermia and HR restores most of the fall in $\dot{V}_{O_2max}$ evoked by heat stress (Nybo *et al.* 2001). Although studies independently altering HR and directly examining cardiac circulation, metabolism and function are required to determine the mechanism, it seems that the decline in SV during maximal exercise is related, at least in part, to the restriction in left ventricular filling time and left ventricular end-diastolic volume that accompanies severe tachycardia and hyperthermia.

In summary, the present findings in trained humans show that systemic and locomotor limb O_2 delivery does not increase linearly from rest to $\dot{V}_{O_2max}$, but plateaus at intensities below $\dot{V}_{O_2max}$, resulting in the blunting of locomotor limb $\dot{V}_{O_2}$ despite the increasing O_2 extraction. Similarly, systemic O_2 delivery and $\dot{V}_{O_2}$ decline during constant load cycling despite the increasing O_2 extraction. In both types of maximal exercise, the impaired systemic O_2 delivery was associated with a decline in SV. The attenuation in LBF blunting leg O_2 delivery and $\dot{V}_{O_2}$ during incremental cycling appears to be largely related to the plateau in $\dot{Q}$ and an enhanced muscle sympathetic vasoconstrictor activity. In contrast to two-legged cycling, LBF and $\dot{V}_{O_2}$ increased until volitional exhaustion during one-legged knee-extensor exercise when O_2 transport was not limited. Collectively, these findings support the hypothesis that restrictions in O_2 supply to locomotor limb muscles impose a limitation to aerobic power and capacity in humans.

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